Refer to: Barrett-Connor E: Current status of the treatment of syphilis. West J Med 122:7-11, Jan 1975

Current Status of the Treatment of Syphilis

ELIZABETH BARRETT-CONNOR, MD, *La Jolla, California*

Penicillin remains the treatment of choice for syphilis, with sustained low blood levels curing virtually all patients having early syphilis and halting disease progression in most patients with symptomatic syphilis. Tetracycline, erythromycin or cephalothin yields similar cure rates for patients with early syphilis who are allergic to penicillin. The efficacy of non-penicillin regimens for the treatment of late syphilis is uncertain. Results of Venereal Disease Research Laboratory (VDRL) or other reagin tests should become negative or remain at very low titer following adequate therapy, although results of Treponema pallidum immobilization (TPI) and fluorescent treponemal antibody-absorbed (FTA-ABS) tests often remain positive.

PENICILLIN, introduced for the treatment of syphilis in 1943,[1] is the drug of choice for the treatment of all stages of the disease. Treponema pallidum is one of the most penicillin-sensitive micro-organisms known and all available evidence suggests that its original sensitivity has not diminished.

A penicillin blood level of 0.03 units per ml is at least ten times that required for experimental inhibition of T. pallidum.[2] The longer the duration of infection, the longer the therapy needed for cure.[3] In very early syphilis, when there are few organisms, transient penicillinemia may be curative. It has recently been shown that a single dose of 2.4 million units of aqueous procaine penicillin G, which produces a blood level greater than 0.03 units per ml for 24 hours, cures incubating seronegative syphilis.[4] A penicillin level of 0.03 units per ml must be sustained for seven to ten days to cure primary and secondary syphilis, while three to four weeks is required for patients with tertiary syphilis.[5]

Because of the necessity for relatively low but sustained penicillinemia, the development of long-acting preparations greatly simplified the treatment of syphilis. A 300,000 unit dose of benzathine penicillin G (Bicillin®) gives 0.03 units per ml blood levels for seven days and the 2.4 million unit dose gives these blood levels for three to four weeks.[6,7] It is therefore possible to treat primary and secondary syphilis with a single injection of 2.4 million units of Bicillin, which is the recommended therapy for primary and secondary syphilis in the United States. In latent syphilis when no spinal fluid examination is done and in tertiary syphilis, a total dose of 9 million units of Bicillin divided over a three-week period is recommended. Any penicillin which produces comparable blood levels of comparable duration can be used. There is no evidence that increasing the dose or duration of

From the Departments of Community Medicine and Medicine, University of California, San Diego, School of Medicine, La Jolla.

Submitted March 15, 1974.

Reprint requests to: E. Barrett-Connor, MD, Department of Community Medicine, University of California, San Diego, School of Medicine, La Jolla, CA 92037.

penicillin therapy above these recommendations improves clinical or serological results.[5]

Recent advances in the treatment of syphilis include the first comprehensive review of the long-term effects of penicillin therapy, and further evaluations of alternate therapy for syphilis in patients allergic to penicillin. New serologic tests which facilitate diagnosis will not be considered here.

Long-term Results of Penicillin Therapy

For an excellent review of the long-term results of penicillin therapy, the reader is referred to a recent supplement of the Bulletin of the World Health Organization published in 1972.[5] In this series, collected from the published literature, 97 percent of 1,381 persons with seronegative primary syphilis were clinically well and serologically negative two to ten years after treatment. The 3 percent "failures" were considered to have been reinfected. Among 1,030 persons with primary seroreactive syphilis, 93 to 100 percent became serologically non-reactive as determined by lipoidal antigen tests. Most or all of the failures were again believed to be due to reinfection. Although reagin tests nearly always reverted to negative, approximately 30 percent of the patients studied retained positive Treponema pallidum immobilization (TPI) after nine years. Similar results were found in 783 patients with secondary syphilis: over 98 percent became seronegative to reagin tests, but nearly 40 percent had persistently positive TPI tests. Most of an additional 2,458 patients with early or early latent syphilis became serologically nonreactive to reagin tests within ten months, and all did so within two years, but only 50 to 70 percent reverted to TPI nonreactivity within the observation period.[8] The absence of a wave of late syphilis following the peak of infectious syphilis occurring during World War II is attributed to the use of penicillin.

The treatment of late latent syphilis appears to be curative although reagin nonreactivity five years after treatment occurs in only 20 to 30 percent of cases, a result comparable with the spontaneous seroconversion achieved in Oslo patients without treatment.[9] Few become nonreactive to TPI tests.[10] In the 469 reported cases of late latent syphilis followed for up to 12 years after treatment with 5 to 15 million units of penicillin, no progression of late latent to late symptomatic syphilis was documented.[5] Further, late symptomatic syphilis has not been reported in any patient who received adequate penicillin therapy before the development of symptomatic syphilis.

The benefit of treatment in patients with established cardiovascular syphilis is difficult to ascertain both because the prognosis depends on the extent of tissue damage at the beginning of treatment[11] and some patients remain asymptomatic and survive to old age without treatment.[12] Nevertheless, most of the 1,168 patients with cardiovascular syphilis reported by 13 investigators were said to have had reduced symptoms or prolongation of life or both.[5] Although aortic regurgitation may first appear after completion of treatment, data are insufficient to attribute this progression to penicillin therapy (therapeutic paradox) or its failure.[13]

Similarly, the benefit of treatment for symptomatic neurosyphilis varies with the amount of disease at the onset of therapy. Most of the 6,902 patients followed for up to 12 years were said to show clinical improvement and a return to or toward normal in the cerebrospinal fluid.[5] However, Wilner and Brody[13] reported that in 25 of 64 patients with general paresis surviving at least ten years after penicillin therapy, new neurologic signs developed. Efficacy is better documented in the treatment of primary optic atrophy, which invariably progresses to blindness without treatment.[8] Although therapy does not reverse changes that have already occurred, early treatment may halt progression and preserve vision in at least 50 percent of cases.[5]

Less than 30 percent of the 8,189 patients with late symptomatic syphilis became seronegative by reagin tests five years after treatment.[5] Most had persistently positive TPI tests. The ability of the host to immobilize treponemes could reflect continued antigenic stimulus by persistent spirochetes. The finding of treponemes in the eyes, brains and lymph nodes of patients treated with penicillin is of great interest but it is as yet without proven clinical significance.[15-17]

Penicillin treatment of the mother earlier than the fourth month of pregnancy prevents congenital syphilis. Later treatment of the mother—actually transplacental treatment of the child—usually prevents congenital syphilis. A most striking failure was the recently reported fatal case in an infant whose mother was treated with penicillin before delivery and who also received massive doses of penicillin after birth.[18] There was no experimental evidence that the treponeme in this

case was resistant to penicillin, and the reason for the treatment failure is unknown.

In congenital syphilis of less than two years' duration, penicillin treatment results in clinical and serological cure in almost all cases, although the conversion to seronegativity may take at least six months.[5] Treatment given for congenital syphilis of more than two years' duration probably prevents later sequelae but the rate of seronegativity is much lower.

The only documented complication of penicillin therapy of syphilis in non-allergic patients is the Jarisch-Herxheimer reaction. This febrile reaction occurs in 50 to 95 percent of patients treated for primary or secondary syphilis, and is seen in early seronegative syphilis as well.[5,10,19,20] The reaction does not appear to be dose-related and there is no evidence that starting with small doses of penicillin or giving bismuth beforehand reduces the frequency of reactions.[19] The Herxheimer reaction is rare in patients with late symptomatic syphilis,[20] but it is here that it is most feared. Aortitis as a complication of therapy is frequently alluded to in the literature, although only seven "fatal Herxheimer reactions" were included in 1,168 patients treated for cardiovascular syphilis.[5] It is difficult to assess the role of treatment in this outcome because sudden deaths occur without therapy and narrowing of the orifice of the coronary arteries has been reported in at least 25 percent of cases in which autopsy was done.[21] Data are inconclusive regarding corticosteroid prophylaxis of Herxheimer reaction during the treatment of late symptomatic syphilis, but many venerologists recommend that steroids be given with antibiotics to patients who have optic or auditory disease.

Alternate Therapy

The incidence of penicillin allergy as reported in venereal disease clinics has not changed in the past 20 years in the United States.[22] Although such reactions are rarely fatal, a history of a penicillin reaction is nearly always a contraindication to the use of the drug for the treatment of syphilis. The efficacy of other antibiotics for treatment of infectious syphilis is relatively well documented, but there is less information about chemotherapy of late syphilis with drugs other than penicillin.[23]

The largest single experience has been with chloramphenicol. As reported by the World Health Organization group, 286 patients with early syphilis received from 10 to 48 grams over a period of six to thirty-six days; 197 became serologically negative within two years and another 18 had reductions in reagin titer.[5] Only nine patients (3 percent) were considered to have had treatment failure. None of nine pregnant patients treated with 20 grams of chloramphenicol over a period of ten days delivered syphilitic babies. In another study 15 patients, five of them pregnant, were cured of early syphilis following 60 mg of chloramphenicol per kilogram of body weight for six to eight days.[24] Dark-field negativity and serologic conversion may not be as prompt as that seen with penicillin but the final results appear to be comparable. The risk of chloramphenicol-associated aplastic anemia precludes its use for the treatment of syphilis except in unusual cases.

Erythromycin is also effective treatment for early syphilis. A study by the United States Department of Health, Education, and Welfare showed that 15 to 20 grams of erythromycin estolate given over ten days failed in 9.2 percent of 261 patients with seronegative primary syphilis and in 4.4 percent of 224 patients with seroreactive secondary syphilis.[25] (The higher failure rate in seronegative syphilis may be explained by reinfection.) Erythromycin estolate does cause occasional hepatotoxicity in adults. Erythromycin base is unassociated with hepatotoxicity but affords lower blood levels. According to Schroeter et al,[26] a 12-month failure rate of 26.8 percent followed the 20 gram schedule. By increasing the dose to 30 grams over the ten-day period, the failure rate at 12 months was reduced to 10.9 percent. Dose efficacy may be related to the weight of the patient, as no definite relapses were noted following the 20 gram dose in 34 patients whose average weight was 120 pounds.[27] Although erythromycin crosses the placental barrier poorly, it has been used successfully for the treatment of pregnant patients with syphilis.[24] Failures have been reported, however, the best documented case being that of South et al,[28] who reported fatal congenital syphilis in an infant whose mother was treated with 15 grams of erythromycin estolate given over a ten-day period two months before delivery.

The treatment of early syphilis with the tetracyclines was reviewed by the WHO group: 163 patients were treated with chlortetracycline, oxytetracycline or tetracycline in doses of from 4 to 70 grams given over periods of seven to twenty-one days.[5] All of the treatment failures occurred in one group of 101 patients receiving 70 grams of chlortetracycline over 11 days.[29] Some of the failures may have been due to variation in drug

potency, as the study was done early in the commercial development of the agent. Other failures were possibly due to the conditions of a concomitant study, apparently in the same patients, demonstrating reduced blood levels when the antibiotic was taken with milk or aluminum-hydroxide-gel. In a more recent study, 30 grams of tetracycline given over a ten-day period cured 90.8 percent of patients with early syphilis.[26] At 24 months, the proportion of cases in which retreatment was necessary (12.7 percent) was not significantly different from that following penicillin (10.7 percent). Most of patients retreated were believed to have reinfection. Moderate to severe gastrointestinal side-effects of tetracycline occurred in 2.3 percent of patients, compared with 11 percent of those treated with erythromycin. Tetracycline is probably the best alternative to penicillin for the treatment of infectious syphilis. At least ten cases in which pregnant women delivered normal babies following tetracycline treatment have been reported,[24-29] and no documented case in which tetracycline failed to prevent congenital syphilis appears in the literature. Nevertheless, because of its effect on the fetus and the danger of hepatotoxicity in pregnant women, tetracycline is a poor choice for the treatment of pregnant patients.

The cephalosporins are the only other adequately tested alternative for the treatment of patients with early syphilis. Duncan and Knox[30] reported that cephalexin, 250 mg twice a day for 15 days, failed in half of 18 patients with early syphilis; although a decrease in titer and healing of primary lesions occurred promptly, secondary syphilis or other evidence of recurrence developed later. On the other hand, possible cephaloridine failures have been reported in only three of at least 45 patients with early syphilis who received 5 to 26 grams over six to fourteen days.[30-35] There were no treatment failures in ten pregnant patients with syphilis. Cephaloridine, which crosses the placenta to yield levels approximately 60 percent of those in maternal blood, may prove to be the treatment of choice for syphilis complicating pregnancy in penicillin-allergic patients.[36] It should be recalled, however, that some allergic patients are also allergic to cephaloridine; and serious reactions, including anaphylaxis, have been reported.[37]

Follow-up

Follow-up of patients treated for early syphilis is based mainly on the use of serologic tests.[38] As was previously indicated, a negative reagin test should be expected in patients with syphilis of less than two years' duration; failure to achieve this result suggests either reinfection or relapse, and is an indication for retreatment. The Venereal Disease Research Laboratory (VDRL) or equivalent test usually reverts to normal within six months to a year in patients treated with penicillin, but may take up to two years in patients apparently adequately treated with other antibiotics. In any case, the titer should be low or falling. In syphilis of more than two years' duration an increasing proportion of patients never become reagin-negative. In such patients titers should be low or decreasing after treatment, but there is no objective endpoint indicative of cure. For this reason it may be advisable to retreat pregnant women who have positive reaction to serologic tests.

The fluorescent treponemal antibody-absorbed (FTA-ABS) test is the most sensitive test available for the diagnosis of all stages of syphilis, but is less useful as a test of cure.[38] Like the TPI test, which it has largely replaced, the FTA-ABS test may remain positive in one-third of patients treated for early seropositive syphilis, and there is at present no evidence to suggest that further treatment is indicated or that symptomatic syphilis will later develop in such patients. Approximately 98 percent of patients with treated late syphilis retain a positive reaction to FTA-ABS test.

In past years it has been recommended that a cerebrospinal fluid examination be done approximately a year after treatment of early syphilis as a further test of cure. This is probably not necessary for seronegative patients who have received an adequate course of penicillin and is no longer recommended by the U.S. Public Health Service; in England all of 1,379 patients who had a spinal fluid examination at least one year after treatment of early syphilis had normal findings.[39] Because less information is available about the prognosis of patients treated with drugs other than penicillin, such patients should have a spinal fluid examination a year after treatment as part of their follow-up.

REFERENCES

1. Mahoney JF, Arnold RC, Harris A: Penicillin in the treatment of early syphilis. Am J Pub Health 33:1387-1391, 1943

2. Turner TB, Hollander DH: Biology of the treponematoses. WHO Monograph Series No 35, 1957

3. Eagle H: The effect of the size of the inoculum and the age of the infection on the curative dose of penicillin in experimental infections with *Streptococci, Pneumococci* and *Treponema pallidum*. J Exp Med 90:595-607, 1949

4. Schroeter AL, Turner RH, Lucas JB, et al: Therapy for

incubating syphilis. Effectiveness of gonorrhea treatment. JAMA 218:711-713, 1971

5. Idsöe O, Guthe T, Willcox RR: Penicillin in the treatment of syphilis: The experience of three decades. Bull WHO, Suppl to Vol 47:1-68, 1972

6. Idsöe O, Guthe T, Christiansen S, et al: A decade of reorientation in the treatment of venereal syphilis. Bull WHO 10:507-561, 1954

7. Putnam LE, Roberts EF: Prolonged blood concentrations of penicillin following intramuscular benzathine penicillin G. Antibiotics & Chemother 4:931-933, 1954

8. Perdrup A: Penicillin treatment of early syphilis: A follow-up study of 213 patients observed for one to eleven years. Acta Derm Venereol (Stockh) 40:340-357, 1960

9. Gjestland T: The Oslo study of untreated syphilis. Acta Derm Venereol (Stockh) [Suppl] 35:Supp 34:11-368, 1955

10. Fiumara NJ: The treatment of syphilis. N Engl J Med 270: 1185-1188, 1964

11. Webster B, et al: Studies in cardiovascular syphilis—III. The natural history of syphilitic aortic insufficiency. Am Heart J 46:117-145, 1953

12. Prewitt TA: Syphilitic aortic insufficiency—Its increased incidence in the elderly. JAMA 211:637-639, 1970

13. Mohr CF, Hahn RD: Therapeutic paradox (?) in cardiovascular syphilis. Am J Syph 36:82-87, 1952

14. Wilner E, Brody GA: Prognosis of general paresis after treatment. Lancet 2:1370-1371, 1968

15. Collart P, Borel LJ, Durel P: Significance of spiral organisms found, after treatment in late human and experimental syphilis. Br J Ven Dis 40:81-89, 1964

16. Smith JL: Spirochetes in late Seronegative Syphilis, Penicillin Nothwithstanding. Springfield, Ill, Charles C Thomas, 1969

17. Yobs AR, Clark JW Jr, Mothershed SE, et al: Further observations on the persistence of treponema pallidum after treatment in rabbits and humans. Br J Vener Dis 44:116-130, 1968

18. Hardy JB, Hardy PH, Oppenheimer EH, et al: Failure of penicillin in a newborn with congenital syphilis. JAMA 212:1345-1349, 1970

19. Heyman A, Sheldon WH, Evans LD: Pathogenesis of Jarisch-Herxheimer reactions; review of clinical and experimental observations. Br J Vener Dis 28:50-60, 1952

20. Willcox RR: A Textbook of Venereal Disease and Treponematoses, 2nd Ed. London, Heinemann Med Books Ltd, 1964

21. Clawson BJ, Bell ET: The heart in syphilitic aortitis. Arch Path Lab Med 4:922-936, 1927

22. Rudolph AH, Price EV: Penicillin reactions among patients in venereal disease clinics—A national survey. JAMA 223:499-501, 1973

23. Montgomery CH, Knox JM: Antibiotics other than penicillin in the treatment of syphilis. N Engl J Med 261:277-280, 1959

24. Taggart SR, Romansky MJ, Landman GS: Treatment of syphilis with aureomycin and chloromycetin. Am J Syph 36:174-178, 1952

25. Brown WJ, Simpson WG, Moore MB, et al: Oral propionyl erythromycin in treating early syphilis. Pub Health Rep 78:911-917, 1963

26. Schroeter AL, Lucas JB, Price EV, et al: Treatment for early syphilis and reactivity of serologic tests. JAMA 221:471-476, 1972

27. Fernando WL: Erythromycin in early syphilis. Br J Vener Dis 45:200-201, 1969

28. South MA, Short DH, Knox JM: Failure of erythromycin estolate therapy in utero syphilis. JAMA 190:70-71, 1964

29. Rodriquez J, Weinstein S, Parkhurst GE: Aureomycin and its effects in early syphilis. Arch Derm 66:59-64, 1952

30. Duncan WC, Knox JM: Cephalosporin antibiotics in venereal disease. Postgrad Med J, Feb Suppl 119-122, 1971

31. Seftel HC, Sieff B, Richardson NJ: Treatment of early syphilis and acute gonorrhoea with cephaloridine (Ceporan). Med Proc 12:29-37, 1966

32. Oller LZ: Cephaloridine in gonorrhea and syphilis. Br J Vener Dis 43:39-47, 1967

33. Flarer F: On the antitreponemic action of cephaloridine. Postgrad Med J 43:Suppl 43, 113-134, 1967

34. Gonzalez-Ochoa A, Moreno JB: The treatment of early syphilis with cephaloridine. Postgrad Med J 43:Suppl 43, 134-135, 1967

35. Glicksman JM, Short DH, Knox JM: Parenteral cephaloridine treatment of patients with early syphilis. Arch Intern Med 121:342-344, 1968

36. Holder WR, Knox JM: Syphilis in pregnancy. Med Clin North AM 56:1151-1160, 1972

37. Kabins SA, Eisenstein B, Cohen S: Anaphylactoid reaction to an initial dose of sodium cephalothin. JAMA 193:165-166, 1965

38. Sparling PF: Diagnosis and treatment of syphilis. N Engl J Med 284:642-653, 1971

39. Jefferiss FJG: Tests of cure in treated early and latent syphilis. Br J Vener Dis 39:139-142, 1963